Progesterone luteal support after ovulation induction and intrauterine insemination: a systematic review and meta-analysis

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Objective: To evaluate the effect of luteal phase P support after ovulation induction IUI.
Design: A systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Undergoing ovulation induction IUI.
Intervention(s): Any form of exogenous P in ovulation induction IUI cycles.
Main Outcome Measure(s): Clinical pregnancy and live birth.
Result(s): Five trials were identified that met inclusion criteria and comprised 1,298 patients undergoing 1,938 cycles. Clinical pregnancy (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.15–1.98) and live birth (OR 2.11, 95% CI 1.21–3.67) were more likely in P-supplemented patients. These findings persisted in analyses evaluating per IUI cycle, per patient, and first cycle only data. In subgroup analysis, patients receiving gonadotropins for ovulation induction had the most increase in clinical pregnancy with P support (OR 1.77, 95% CI 1.20–2.6). Conversely, patients receiving clomiphene citrate (CC) for ovulation induction showed no difference in clinical pregnancy with P support (OR 0.89, 95% CI 0.47–1.67).
Conclusion(s): Progesterone luteal phase support may be of benefit to patients undergoing ovulation induction with gonadotropins in IUI cycles. Progesterone support did not benefit patients undergoing ovulation induction with CC, suggesting a potential difference in endogenous luteal phase function depending on the method of ovulation induction. (Fertil Steril® 2013;100:1373–80. ©2013 by American Society for Reproductive Medicine.)
Key Words: Progesterone, luteal support, ovulation induction, intrauterine insemination

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Implantation of the developing blastocyst occurs during the luteal phase of the menstrual cycle when the endometrium is under the direct influence of P. Progesterone production and release is achieved through a complex pathway in which pulsatile secretion of gonadotropin-releasing hormone from the hypothalamus acts at the level of the pituitary to release LH, which in turn stimulates production and release of P from the corpus luteum (CL). Progesterone is required for endometrial receptivity by inducing secretory changes and up-regulation of implantation factors (1).

Iatrogenic disruptions in the hypothalamic-pituitary-gonadal axis may occur during ovulation induction and controlled ovarian hyperstimulation (COH) (2), manifested by a shortened

Received May 6, 2013; revised May 30, 2013; accepted June 19, 2013; published online July 19, 2013.
M.J.H. has nothing to disclose. B.W.W. has nothing to disclose. T.D.L. has nothing to disclose. M.W. has nothing to disclose. N.T. has nothing to disclose. A.H.D. has nothing to disclose. E.D.L. has nothing to disclose. A.M.P. has nothing to disclose.
Supported, in part, by the Program in Reproductive and Adult Endocrinology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland.
The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of Defense or the U. S. Government.
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Fertility and Sterility® Vol. 100, No. 5, November 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.06.034

luteal phase with low concentrations of P. One report (3) suggests that as many as 20% of women undergoing gonadotropin-stimulated ovulation induction experience luteal phase defects. Ultimately, alterations in the luteal phase create suboptimal environments for blastocysts implantation and maintenance of early pregnancy (2). Several prospective randomized controlled trials have evaluated the benefits of luteal phase P support in ovulation induction cycles, but the results have been conflicting with some trials showing a benefit and others no benefit (4–8).

This systematic review and meta-analysis was performed to summarize the available published randomized controlled trial data regarding the use of luteal phase P support in patients undergoing ovulation induction with IUI.

MATERIALS AND METHODS

Study Design

This study was a systematic review and meta-analysis. An a priori protocol was written and agreed to by the first and senior authors before initiation of the study, to include study design, inclusion and exclusion criteria, primary outcomes, statistical methods, and bias assessment.

Literature Search

Literature searches were conducted to retrieve randomized controlled trials comparing the use of luteal phase exogenous P support versus no P support in patients undergoing ovulation induction IUI cycles. Databases searched included PubMed and Embase. Additional literature searches were performed on the references from identified studies. The searches were not limited by language or by date and were executed between January 5 and 8, 2013. Searches used keywords and specific database indexing terminology when available (Supplemental Addendum, available online).

Study Selection

Criteria for inclusion in the study were established before the literature search in a written protocol. Inclusion was limited to studies that were published randomized controlled trials, compared luteal phase exogenous P versus no P in ovulation induction IUI cycles, and included study participants who were infertile or subfertile. Any type of exogenous P was allowed, including IM, oral, and any form of vaginal administration. Any type of ovulation induction was allowed, including clomiphene citrate (CC), exogenous gonadotropins, hCG, and aromatase inhibitors. Publication in any language was allowed. Exclusion criteria included nonrandomization, timed intercourse cycles, natural cycles, and publication as abstract only, meeting proceeding, book chapter, or review article. The studies were screened independently in parallel by two investigators (M.J.H. and A.M.P.) and there were no disagreements in the studies identified for inclusion. The search strategy yielded 32 publications before duplication removal. Searches executed in the other databases and studies identified from the references of other articles added an additional four studies for a total of 25 studies after duplication removal (Supplemental Fig. 1, available online). The 25 abstracts were reviewed and 14 records were excluded during this review for failure to meet inclusion criteria based on data presented in the abstract. Nine full text articles were evaluated for inclusion and exclusion criteria. Of these, five articles met full inclusion criteria. One meeting abstract was fully published in a trial included in the analysis (4) and three studies (9–11) were excluded for having luteal support other than P. Study quality and the potential for bias within each study was also ascertained, specifically evaluating for randomization method, concealment of allocation, blinding of providers and patients, and flow of patients through the randomization, treatment, and outcome stages.

Data Collection

Data were abstracted in parallel by two authors (M.J.H. and A.M.P.). Outcomes data (clinical pregnancy, ongoing pregnancy, live birth, and miscarriage) were extracted from the source articles in the form of 2×2 tables based on intent-to-treat results. When intent-to-treat results were not reported, data were extracted from the provided per-protocol results. Continuous data (age and duration of infertility) were extracted in the form of mean, SD, and population size. Additional extracted data included author, year of publication, journal, country of origin, randomization method, sample size, number of patients randomized, number of cycles performed, method of ovulation induction, type of P support, duration of P support, method of ovulation triggering, trial registry, and the reporting of conflicts of interest. Primary outcomes were clinical pregnancy and live birth. The secondary outcome was miscarriage. Data were collected from per patient and per cycle outcomes. In studies allowing multiple cycles, data from the first cycle were also extracted when reported.

Data Synthesis

Data for synthesis was based on intent-to-treat results when provided. The primary analyses were done using per cycle data. Additional sensitivity analyses were performed using per patient and per first cycle data to control for possible unit of analysis biases (12, 13).

Heterogeneity was evaluated using the Q test and reported as the Q value and *P* value. Heterogeneity was also evaluated using I^2 index values and reported for each outcome as percentages with 95% confidence intervals (CI) when three or more studies were available for comparison (95% CI were not available for synthesis of only two studies). Due to the small number of studies available for meta-analysis and to avoid tenuous common-effect assumptions, a random effects model was used for all primary analyses (14). In addition, fixed-effects models were performed as secondary analyses and for comparison. Bias was assessed at the study level using a qualitative review assessing randomization, concealment, blinding, and patient flow. Publication bias was assessed at the outcome level by visual inspection of funnel plots. Dichotomous outcome data were reported as odds ratios (OR) with 95% CI. Continuous data were synthesized using weighted means with 95% CI. A priori subgroup

analyses were planned to compare the types of P support and methods of ovulation induction. Sensitivity analyses were planned a priori if included trials were found to be at high risk of bias at either the study or outcome level.

Data collection was performed in Excel (Microsoft Office 2007) and statistical analysis was performed using Mix 2.0 Pro (Bax L: MIX 2.0. Professional software for meta-analysis in Excel, version 2.0.1.4. BiostatXL, 2011; http://www.meta-analysis-made-easy.com). This study was Institutional Review Board exempt given the nature of the work.

RESULTS

Studies Included for Systematic Review and Meta-analysis

A total of 25 abstracts were identified, 9 full text articles were reviewed, and from these 5 trials met full inclusion criteria (Supplemental Fig. 1) (4–8). The five trials comprised 1,298 patients undergoing 1,938 ovulation induction IUI cycles. All five studies specifically described inclusion criteria consistent with or explicit for unexplained infertility. Two studies used gonadotropins in the form of exogenous recombinant FSH for ovulation induction (6, 7), one study used CC plus hMG (5), one study used only CC (8), and one study used either CC or letrozole in all patients with some patients also receiving hMG (4) (Table 1). Ovulation triggering was performed with either 5,000 or 10,000 units of hCG in all studies, although no studies specified whether the route of administration was SC or IM. None of the included studies used IM or oral P and all studies used vaginal routes of P with differing protocols of P type, dose, and starting and stopping times (Table 1).

Assessment of Bias Risk

Assessment of bias within each individual trial showed that all reported the randomization process clearly. However, only three trials used computer generated randomization sequences in a noncrossover design (4, 6, 8) (Supplemental Table 1, available online). Another trial used a computer generated randomization sequence; however, patients were randomized to their first cycle of treatment and alternated treatment groups in each subsequent treatment cycle (7). The final trial reported sequential randomization of patients (5). Only one trial detailed specific attempts to control for allocation concealment (6). None of the trials documented blinding of the physicians or patients, none used placebo control, and none documented blinding of outcomes data (Table 2). Four trials adequately reported on the flow of patients through the study and were at low risk of incomplete data reporting (4, 6–8). There was no pharmaceutical support disclosed in any of the trials.

None of the studies demonstrated baseline differences between the two randomized groups with regard to age, duration of infertility, or infertility diagnosis. Body mass index (BMI) was not reported in any of the trials. Primary infertility and parity were inconsistently reported in the articles, but no statistical differences were reported in any

TABLE 1

Study characteristics of trials meeting inclusion in the systematic review.

Authors	Country of study	Patients	Ovarian stimulation	Progesterone supplementation	Ovulation triggering	No. of cycles allowed
Erdem et al. 2009 (6)	Turkey	Unexplained infertility	75 IU FSH starting on cycle day 3	Crinone 8% post-IUI day 2 through 12 weeks	10,000 units hCG	Up to 3
Kyrou et al. 2010 (8)	Belgium	Normo-ovulatory/ unexplained	50 mg CC on cycle days 3–7	Utrogestan 200 mg in 3 separate doses post-IUI day 1 through 7 weeks	5,000 units hCG	1
Ebrahami et al. 2010 (5)	Iran	Unexplained infertility	50 mg CC BID on cycle days 3–7 plus 75 IU hMG on cycle days 7–9	Cyclogest 400 mg daily post-IUI day 2 through 10 weeks	5,000 units hCG	Up to 3
Maher 2011 (7)	Egypt	Unexplained infertility	75 IU FSH starting days 2–5	Crinone 8% post-IUI day 1 through 14 days	10,000 units hCG	Up to 6, patients alternated treatment groups each cycle
Agha-Hosseini et al. 2012 (4)	Iran	Unexplained infertility	Either 50 mg CC BID or letrozole 5 mg daily on cycle days 3–7, with or without 75 IU hMG days 3–7	Cyclogest 400 mg post-IUI day 1 through 14 days	10,000 units hCG	1

Note: CC = clomiphene citrate.

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TABLE 2

Primary pregnancy outcomes in the five included randomized controlled trials reported on a per cycle basis.

Study	Group	Patients (n)	Cycles (n)	Positive hCG	*P* value	Clinical pregnancy	*P* value	Live birth	*P* value
Erdem et al. 2009 (6)	P	109	223	25.1%	.002	21.2%	.028	17.4%	.016
	Control	105	204	13.7%		12.7%		9.3%	
Kyrou et al. 2010 (8)	P	243	243	NR	NR	7.3%[a]	NS	NR	NR
	Control	225	225	NR		8.7%[a]		NR	
Ebrahami et al. 2010 (5)	P	98	252	13.5%	NS	11.5%	NS	7.5%	NS
	Control	102	259	11.2%		10.0%		5.7%	
Maher 2011 (7)	P	37[b]	132	37.1%	.004	29.5%	.07	18.9%	<.001
	Control	34[b]	126	20.6%		19.8%		5.5%	
Agha-Hosseini et al. 2012 (4)	P	148	148	29.0%	NS	24.3%	.02	NR	NR
	Control	142	142	21.8%		14.1%		NR	

Note: NR = not reported; NS = not significant.
[a] Values reported as ongoing pregnancy (intrauterine fetal cardiac activity after 12 weeks gestation).
[b] Other studies reporting gestational sac on ultrasound.

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article (Supplemental Table 2, available online). Diminished ovarian reserve was an explicit exclusion criteria in all five articles, although the FSH cutoff for diminished ovarian reserve varied from >10 to >15 IU/L between the studies. Ovarian reserved, measured by day 3 FSH level, was reported in four trials and the mean reported levels in the randomized groups varied between 5.1 and 7.3 IU/L in the four studies (Supplemental Table 2). There was no difference in ovarian reserve between the two groups in any study. Only one study reported peak E_2 levels, which were similar between the two groups. Four studies reported on the number of dominant follicles measured by ultrasound (>16–17 mm) and there were no differences reported between the two groups. No studies reported significant differences between the groups in the total dose of ovulation medication received or the days of stimulation. Only one study reported a statistical difference in the stimulation results between the two groups, with patients in the P group having a small but statistically significant fewer number of follicles ≥17 mm on the day of hCG (P supplemented: 1.2 vs. P not supplemented: 1.3, P=.02) (8). There was no evidence of publication bias with funnel plot analysis (Supplemental Fig. 2, available online).

Comparison of Clinical Pregnancy

Four trials reported clinical pregnancy rates (PRs) (gestational sac on transvaginal ultrasound) and one trial reported ongoing PRs (intrauterine fetus with cardiac activity after 12 weeks gestation) (8). Two trials reported statistically higher clinical pregnancy in patients receiving P support versus those without P support (6, 7) (Table 2). There was wide variation between the studies in the clinical PR per patient (7%–55%) and in the clinical PR per cycle (7%–30%) (Table 2). All five studies reported clinical PRs on a per cycle basis. Meta-analysis of 1,938 cycles demonstrated that the likelihood of clinical pregnancy per cycle was increased with the use of P support (OR 1.49, 95% CI 1.15–1.98) (Fig. 1A). Minimal heterogeneity was suggested by the results of the Q test (Q = 5.0, P=.28) and the I^2 index (I^2 value = 20%, 95% CI 0–83%).

Comparison of Live Birth

Only three of the trials reported on live birth rates (5–7). Two trials reported increased live birth rates in patients receiving P support and the other trial reported no significant difference between the groups (Table 2). There was wide variation between the studies in the live birth rates per patient (10%–36%) and less variation in the live birth rates per cycle (6%–19%) (Table 2). All three trials reported on live birth rate per cycle (5–7). Meta-analysis of 1,196 cycles demonstrated that the likelihood of live birth was increased with the use of P support (OR 2.11, 95% CI 1.21–3.67) (Fig. 1B). Moderate heterogeneity was suggested by the results of the Q test (Q = 3.6, P=.15) and the I^2 index (I^2 value = 45%, 95% CI 0–94%).

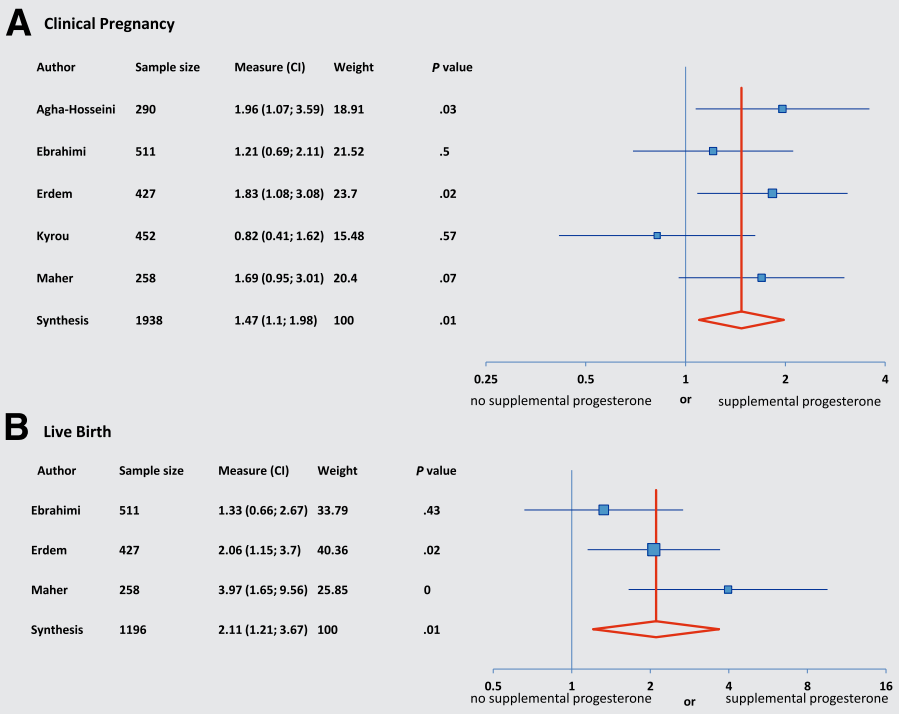
Comparison of Miscarriage

Three trials reported on miscarriage rates and the miscarriage rates were similar between the two groups in every study (4, 7, 8). There was no significant difference in miscarriage per cycle between the two groups (OR 1.03, 95% CI 0.52–2.04). No heterogeneity was suggested by the results of the Q test (Q = 0.09, P=.80) and the I^2 index (I^2 value = 0, 95% CI 0–12%).

Subgroup Analysis

The a priori subgroup analysis was performed based on the method of ovulation induction. In the two trials using only gonadotropins (75 IU FSH), the likelihood of clinical pregnancy per cycle was increased in patients receiving P support (OR 1.77, 95% CI 1.20–2.60) (Fig. 2A). No heterogeneity was suggested by the results of the Q test (Q = 0.03, P=.87) and the I^2 index (I^2 value = 0). In the same gonadotropin studies, the likelihood of live birth per cycle was increased in patients receiving P support (OR 2.63, 95% CI 1.42–4.80) (Supplemental Fig. 3, available online). No heterogeneity was suggested by the results of the Q test (Q = 1.4, P=.23) and the I^2 index (I^2 value = 29%). Based on these data, the number of patients needed to treat with P to have one additional live birth per cycle when using recombinant FSH for ovulation induction was five. Two studies reported on patients receiving CC for ovulation induction, with

FIGURE 1



Forrest plot of (A) clinical pregnancy and (B) live birth. CI = confidence interval.

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Agha-Hosseini et al. (4) reporting this as a subgroup analysis of their larger study. There was no benefit in clinical pregnancy per cycle with P support in patients receiving CC (OR 0.89, 95% CI 0.47–1.67) (Fig. 2B). No heterogeneity was suggested by the results of the Q test (Q = 0.36, P=.63) and the I^2 index (I^2 value = 0). There was not data on live birth to perform statistical synthesis of live birth for CC only. Finally, two studies reported on patients receiving CC followed by 3 days of hMG, with Agha-Hosseini et al. (4) reporting this as a subgroup analysis of their larger study. There was no benefit in clinical pregnancy per cycle with P support in patients receiving combined CC and hMG (OR 1.34, 95% CI 0.81–2.23) (Fig. 2C). No heterogeneity was suggested by the results of the Q test (Q = 0.79, P=.43) and the I^2 index (I^2 value = 0). Only one study (5) reported on live birth using CC with hMG and found no significant difference in live birth rates per patient (P support: 19.4% vs. no P support 14.7%).

The planned a priori subgroup analysis based on route of P was not performed as no trials reported using IM or oral routes of administration. The five trials used three different forms of vaginal P, which varied as to time of initiation, dose, and duration of administration. The lack of similarity with any of the regimens precluded subgroup analysis of P administration.

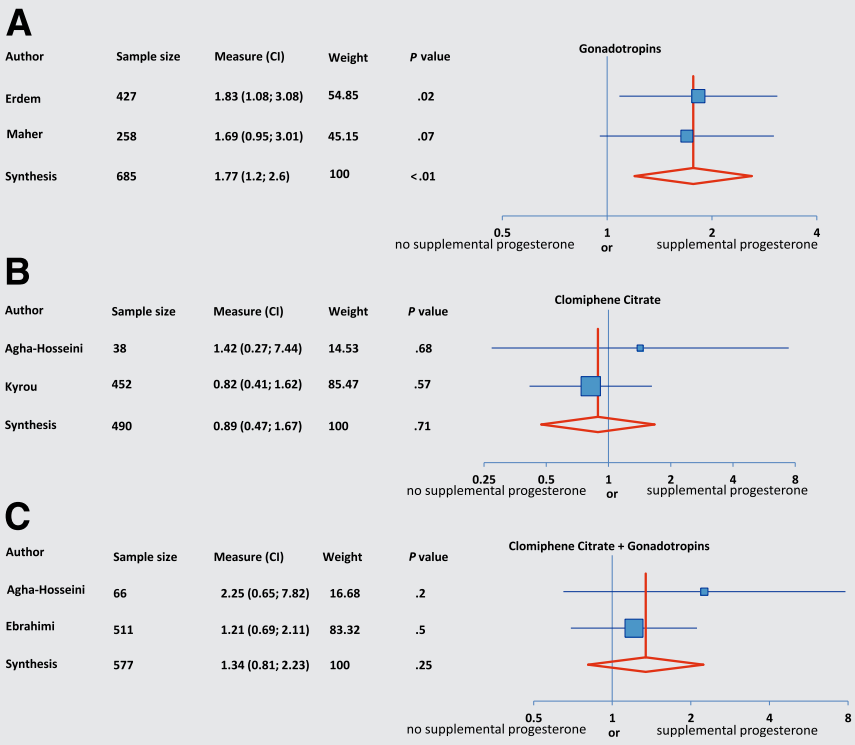
Sensitivity Analysis

Sensitivity analyses were performed per patient and first cycle only to control for potential unit of analysis bias. The likelihood of clinical pregnancy per patient was increased with the use of P support (OR 1.59, 95% CI 1.18–2.27). Moderate heterogeneity was suggested by the results of the Q test (Q = 6.3, P=.17) and the I^2 index (I^2 value = 37%, 95% CI 0–76%). Four studies reported clinical PRs in the first cycle (4, 6–8). The clinical PRs were statistically similar in the first cycles in all four articles. There was a trend toward increased likelihood of clinical pregnancy in first cycles with the use of P (OR 1.71, 95% CI 0.98–2.98), although it was not statistically significant (P=.06). Moderate heterogeneity was suggested by the results of the Q test (Q = 6.4, P=.09) and the I^2 index (I^2 value = 53%, 95% CI 0 84%).

In the sensitivity analysis of live birth per patient, the use of P support was associated with increased likelihood of live birth (OR 2.48, 95% CI 1.29–4.77). Moderate heterogeneity was suggested by the results of the Q test (Q = 4.4, P=.10) and the I^2 index (I^2 value = 55%, 95% CI 0–87%). Only two studies reported live birth rates in the first cycle (6, 7). Maher (7) reported a higher live birth rate with P support in the first cycle (P supplemented: 27% vs. P not supplemented: 8.8%, P=.04). Similarly, Erdem et al. (6) reported a higher live birth rate with P support in the first cycle (P supplemented: 9.5% vs. P not supplemented: 6.6%, P<.01). The likelihood of live birth was increased with the use of P support in first cycles (OR 3.76, 95% CI 1.77–7.99). No heterogeneity was suggested by the results of the Q test (Q <0.001, P=.98) and the I^2 index (I^2 value = 0).

A sensitivity analysis was performed excluding the Maher (7) trial for potential risk of bias regarding the randomization methods. This trial was exlcude for alternating patients

FIGURE 2



Forrest plot of clinical pregnancy in subgroup analysis based on method of ovulation induction. (A) gonadotropins; (B) clomiphene citrate; (C) clomiphene citrate + gonadotropins. CI = confidence interval.

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between treatment groups on every cycle. The likelihood of clinical pregnancy per cycle was increased with P use (OR 1.20, 95% CI 1.10–2.04). Moderate heterogeneity was suggested by the results of the Q test (Q = 4.7, *P*=.15) and the I^2 index (I^2 value = 42%, 95% CI 0–90%). In the same sensitivity analysis, the likelihood of live birth per cycle was increased with P use (OR 1.93, 95% CI 1.08–3.45). Minimal heterogeneity was suggested by the results of the Q test (Q = 1.4, *P*=.23) and the I^2 index (I^2 value = 29%).

In fixed-effect models performed as secondary sensitivity analyses, similar point estimates, interval estimates, and *P* values were observed.

DISCUSSION

The role of exogenous P support in the luteal phase of IUI cycles has been controversial. Luteal phase dysfunction is associated with inadequate production of P resulting in endometrial developmental failure or asynchronicity between the embryo and endometrium, essential in both implantation and maintenance of early pregnancy (5, 15). Progesterone and hCG have been studied to improve luteal phase support in IUI cycles. However, P may be the preferred choice due to the increased risk of ovarian hyperstimulation syndrome (OHSS) with hCG (16). The results of this meta-analysis demonstrate an overall benefit to the use of P support in the luteal phase of IUI cycles. These findings persisted in multiple sensitivity analysis controlling for different units of analysis and potential bias. In subgroup analysis, the benefit of P luteal support was found to only occur in cycles where ovulation induction was achieved with exogenous gonadotropins and not in cycles with CC.

There is biological plausibility and clinical evidence to suggest that exogenous gonadotropins and CC may have differing effects on endogenous luteal phase function. The effect of exogenous gonadotropins directly on the ovaries leads to increased serum E_2 and negative feedback on the hypothalamic-pituitary-ovarian axis (17, 18). This ultimately may lead to aberrant LH pulsitility and P secretion from the CL (19, 20). This feedback loop has been proposed as a mechanism of luteal phase dysfunction in gonadotropin-stimulated cycles (18, 21–23). Luteal phase deficiency may occur in 12%–20% of gonadotropin cycles (3, 24) and is consistent with Erdem et al. (6) reporting a decreased mean luteal length of 11 days in non-P supported gonadotropin cycles. These studies provide evidence that the luteal phase may be compromised in gonadotropin ovulation induction cycles and the results of this meta-analysis and the included randomized controlled trials suggest that supporting the luteal phase with exogenous P increases clinical pregnancy and live birth (5–7).

Compared with the decrease in luteal LH concentrations in gonadotropin cycles, CC increases LH levels (25), even if

GnRH antagonists are co-administered (26). This results in a dose-responsive positive relationship between estrogen (E) and P levels in the luteal phase with CC administration (8, 15, 27). The potential for CC treatment to increase CL function has led to its proposal as a treatment modality for patients with inadequate luteal phase endogenous P secretion (15). There is significant evidence to suggest that endogenous CL function may be decreased in gonadotropin cycles and enhanced in CC cycles. This may explain the findings of this meta-analysis that gonadotropin IUI cycles may benefit from P support, whereas CC cycles do not.

The strengths of this study are the inclusion of randomized controlled trials, the comprehensive literature search, and the multiple sensitivity analyses. The sensitivity analyses were performed to control for the fact that the studies varied on the number of cycles each patient was allowed to undergo (1–6 cycles), which introduces potential unit of analysis bias into the results of the meta-analysis (12). The results of the present study remained consistent in all the sensitivity analyses, indicating that unit of analysis bias did not impact the results. Potential weaknesses of the study resulted primarily from the significant heterogeneity in the methodology of the included randomized controlled trials, with significant heterogeneity in the type of ovulation induction, the dose of hCG for ovulation triggering, and the dosing, starting time, pharmacologic type, and duration of vaginal P support. The heterogeneity of the five studies was clearly demonstrated in the Q and I^2 index testing and should be considered when interpreting the results of the meta-analysis. We attempted to control for this clinical heterogeneity by performing all analyses using a random effects model, even if the Q test and I^2 index suggested minimal statistical heterogeneity. The random effects model accounts for this interstudy heterogeneity by estimating the mean of a distribution of multiple effects (28). This results in the random effects model having a larger variance, SE, and CI for the summary effect than a fixed effects model would give (28). Despite the wider CIs in this model, the results of the present study remained statistically significant. In addition, secondary sensitivity analysis using fixed-effect models did not significantly alter any of the point estimates. Furthermore, we performed subgroup analysis on the type of ovulation induction, which clearly demonstrated the beneficial effect of luteal phase P support derived from studies using gonadotropins for ovulation induction. Another potential weakness was in the design of the randomized controlled trials, which were all open-label trials. Open-label trials may be subject to potential bias due to physician and patient awareness of treatment allocation (29) and there is meta-epidemiologic evidence to suggest that unclear allocation concealment or lack or blinding may cause overoptimistic estimates of treatment effects (30). Despite this potential bias, given appropriate randomization and objective outcomes measures, such as live birth, this is unlikely to significantly impact estimates. Another potential weakness was the inconsistent reporting of baseline patient characteristics and peak E_2 levels in the studies. Although the data reported in the trials were similar for baseline characteristics and stimulation parameters, it is possible that unreported or unmeasured differences between the groups existed despite randomization.

In conclusion, the results of this systematic review and meta-analysis suggest that luteal phase P support improved the likelihood of clinical pregnancy and live birth in IUI cycles where ovulation induction was achieved with gonadotropins. Conversely, P support did not benefit patients undergoing ovulation induction with CC, suggesting a potential difference in endogenous luteal phase function depending on the method of ovulation induction. Utilization of luteal phase P support in gonadotropin IUI cycles seems warranted. There is a need for additional large, multicenter randomized trials to confirm these findings, establish a cost benefit, and determine the duration of P that is necessary to see clinical benefit.

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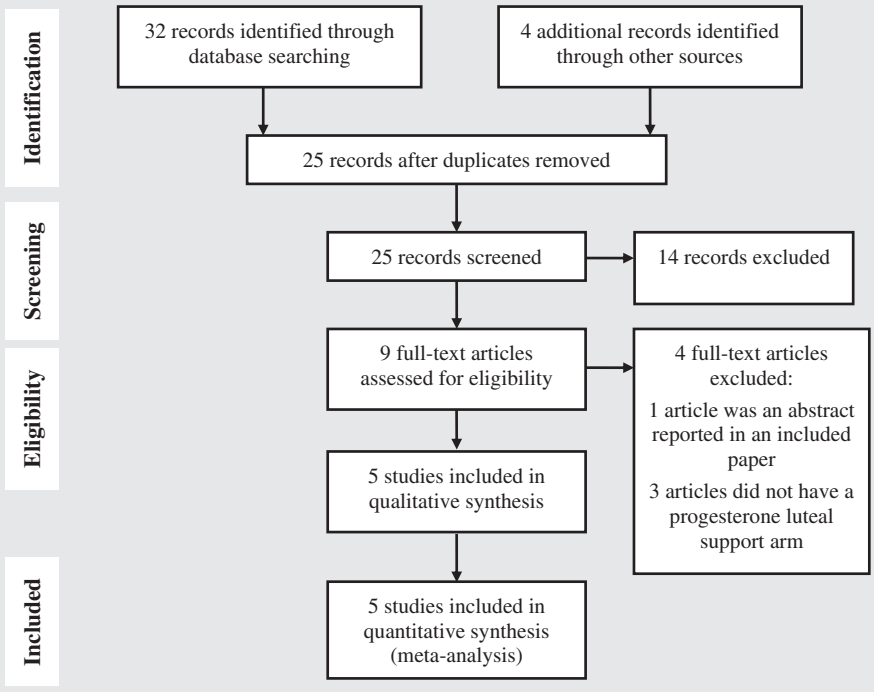
DETAILED SEARCH STRATEGY

The following search strategy was performed: (((((“vaginal progesterone”[tiab] OR progesterone[tiab] OR progesterone [mh])) AND (“luteal support”[tiab] OR luteal phase[mh] OR “luteal phase”[tiab])) AND (“intrauterine insemination”[tiab] OR IUI[tiab] OR insemination, artificial[mh] OR ovulation induction[mh] OR “ovarian stimulation”[tiab]))) AND (randomized controlled trial[pt] OR randomized controlled trial[mh] OR single-blind method[mh] OR double-blind method[mh] OR random allocation[mh] OR random*[tiab] OR “single blind”[tiab] OR “double blind”[tiab] OR placebo[tiab] OR “randomized controlled trial”[tiab] OR controlled clinical trial[pt] OR “controlled clinical trial”[tiab] OR (doubl*[tiab] AND blind*[tiab]) OR (single*[tiab] AND blind*[tiab])).

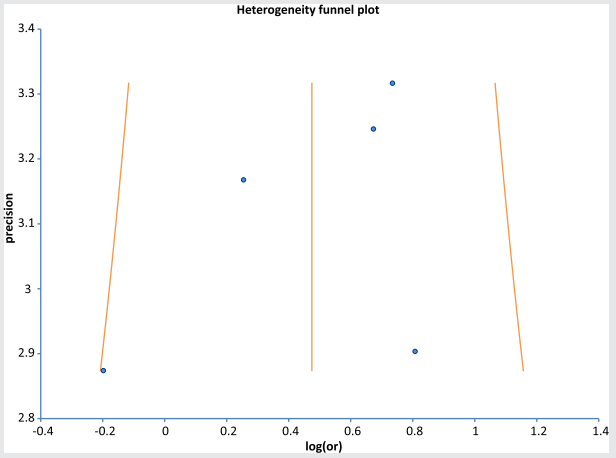
SUPPLEMENTAL FIGURE 1



PRISMA flow diagram of study selection.

Hill. Progesterone luteal support for IUIs. Fertil Steril 2013.

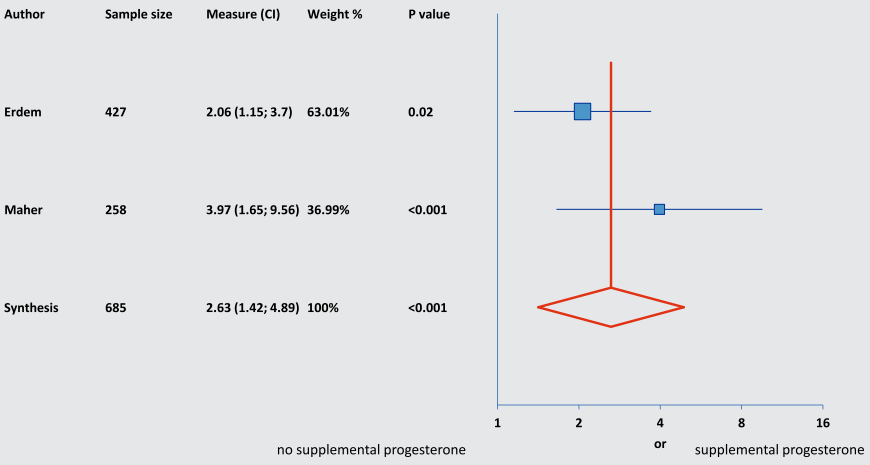
SUPPLEMENTAL FIGURE 2



Funnel plot assessment of publication bias.

Hill. Progesterone luteal support for IUIs. Fertil Steril 2013.

SUPPLEMENTAL FIGURE 3



Forrest plot of live birth in subgroup analysis in patients receiving gonadotropin ovulation induction. CI = confidence interval.

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SUPPLEMENTAL TABLE 1

Assessment of bias in the included randomized controlled trials including assessments of randomization, allocation concealment, blinding, data reporting, and declaration of conflicts of interest.

Authors	Randomization	Allocation concealment	Blinding of participants	Blinding of outcomes	Incomplete data reporting	Analysis type	Conflicts of interest or pharma sponsorship	Trial registry
Erdem et al. 2009 (6)	Software generated random sequence	Single author aware, treating authors blinded	None	None	Yes	Intent to treat	None	Not stated
Kyrou et al. 2010 (8)	Software generated random sequence	None	None	None	Yes	Intent to treat and per protocol	Not stated	Yes
Ebrahami et al. 2010 (5)	Sequentially randomization	None	None	None	None	Per protocol	None	Yes
Maher 2011 (7)	Software generated random sequence, patient's alternated treatment arms every subsequent cycle	None	None	None	Yes	Per protocol	Not stated	Not stated
Agha-Hosseini et al. 2012 (4)	Software generated random sequence	None	None	None	Yes	Per protocol	Not stated	Yes

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SUPPLEMENTAL TABLE 2

Fertility history, ovarian reserve, and stimulation results reported between the studies.

Study	Group	Age (y)	*P* value	Primary infertility	*P* value	Day 3 FSH (IU/L)	*P* value	Peak E_2 (pg/mL)	*P* value	Dominant follicles[a]	*P* value
Erdem et al. 2009 (6)	P	30.0 ± 4.8	NS	64.2%	NS	7.3 ± 2.7	NS	NR	NR	1.6 ± 0.6	NS
	Control	29.7 ± 4.3		63.8%		7.0 ± 2.7		NR		1.5 ± 0.9	
Kyrou et al. 2010 (8)	P	32.1 ± 3.6	NS	71.4%	NS	5.4 ± 3.1	NS	513.0 ± 248.0	NS	1.2 ± 0.3	NS
	Control	32.2 ± 3.9		69.6%		5.1 ± 2.1		504.0 ± 306.0		1.3 ± 0.4	
Ebrahami et al. 2010 (5)	P	27.9 ± 3.3	NS	NR	NR	6.1 ± 2.7	NS	NR	NR	2.0 ± 0.7	NS
	Control	28.4 ± 4.1		NR		6.7 ± 2.0		NR		2.2 ± 0.8	
Maher 2011 (7)	P	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Control	NR		NR		NR		NR		NR	
Agha-Hosseini et al. 2012 (4)	P	27.4 ± 3.7	NS	NR	NR	5.4 ± 3.1	NS	NR	NR	1.6 ± 0.7	NS
	Control	26.8 ± 3.6		NR		5.1 ± 2.1		NR		1.4 ± 0.8	

Note: NR = not reported; NS = not significant.
[a] Defined as follicles more than 16 or 17 mm.

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